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Tudor Calistru *

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New therapeutic challenges in metastatic breast cancer: the association of CDK4 / 6 inhibitors with radiotherapy. A short review

Emil Anton[1,3], Bogdan Doroftei[1,3], Ciprian Ilea[3], Bolota Mariana[3], Delia Nicolaiciuc[3], Radu Maftei[1,3], Gabriela Simionescu[1,3], Tudor Calistru[5], Carmen Rodica Anton[2,4]

[1]Department of Obstetrics and Gynecology, University of Medicine and Pharmacy, Gr. T. Popa", Iasi | UMF Iasi, No. 16 University Street, Iasi, Romania

[2]Department of Internal Medicine (Gastroenterology), University of Medicine and Pharmacy, Gr.T. Popa", Iasi | UMF Iasi, No. 16 University Street, Iasi, Romania

[3]Cuza-Voda Obstetrics and Gynecology Hospital, No. 34 Cuza-Voda Street, Iasi, Romania

[4]Saint Spiridon Emergency Clinical Hospital, No.1 Independence Boulevard, Iasi, Romania

[5]University of Medicine and Pharmacy, Gr.T. Popa" Doctoral School Department, No. 16 University Street, Iasi, Romania

***Corresponding Author:** Tudor Calistru, University of Medicine and Pharmacy, Gr.T. Popa" Doctoral School Department, No. 16 University Street, Iasi, Romania.

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Abstract

FDA approval of CDK4 / 6 inhibitors (Palbociclib, Ribociclib and Abemaciclib) for metastatic and advanced breast cancer, in combination or not with Fulvestrant or Letrozole, has improved the prognosis of this type of patient population. Palliative radiotherapy with antalgic purpose in most of the cases is often part of the multidisciplinary treatment of bone involvement metastatic breast cancer. In the context of the approval of these innovative therapies and of the development of radiotherapy techniques, including stereotactic radiosurgery, it is necessary to identify the best therapeutic sequence and parameters (dose, volume, fraction size) to obtain a synergistic effect. Considering the toxicity profiles of new therapies (especially lymphopenia and neutropenia) and the different mechanisms of the induction of these toxicities towards radiotherapy and chemotherapy, it is also necessary to demonstrate the safety profile of concomitant or sequential irradiation with the administration of CDK4 / 6 inhibitors in combination with radiation therapy.

Keywords: CDK4/6, metastatic breast cancer, radiotherapy

Background

Breast cancer is the most common type of female malignancy. Worldwide cancer mortality in women remains high despite the achievements made in diagnosis and treatment. Breast cancer genome sequencing has identified five distinct molecular subtypes, including luminal A, luminal B, human epidermal growth factor receptor (HER2), basal and low claudin, luminal subtypes are characterized by the typical expression of the estrogen receptor (ER) and / or the progesterone receptor (PR), providing the opportunity for hormonal and andocrine therapy. Intrinsic resistance or tolerance to hormone therapy is a cause of treatment failure in this subtype of tumors. Basal-like breast cancer, characterized by the relatively aggressive and absent phenotype of ER, PR, and HER2, also requires the identification of therapy therapies for enhancing prognosis. Following pre-clinical studies, cyclin-dependent kinase inhibitors 4/6 (CDK4 / 6) (Palbociclib, Ribociclib, and Abemaciclib) were approved in combination with aromatase inhibitors (AI) or fulvestrant for metastatic breast cancer (MBC) [1].

The cyclin-dependent family of kinases (CDKs) are regulators of cell cycle progression and cyclin D is a transcriptional target of the estrogen receptor (ER) and its interaction with CDK4 / 6 modulates through the retinoblastoma gene (Rb) the passage of cells from G1 to S phase. Three innovative molecules: Palbociclib (Ibrance, Pfizer, New York, USA), Ribociclib (Kisquali, Novartis, Basel, Switzerland) and Abemaciclib (Verzenio, Eli Lilly, Indianapolis, (ribociclib) were evaluated in the PALOMA (palbociclib), MONALEESA (ribociclib) and MONARCH (abemaciclib) studies in metastatic breast cancer [2].

Palbociclib is the first of the (CDK 4/6) inhibitors, approved in association with endocrine therapy, for patients with advanced breast cancer progressing on endocrine therapy after evaluation of the PALOMA-3 trial. PALOMA-3 randomly assigned 521 patients with advanced HER2-negative breast cancer with hormone receptor positive after disease progression in 2:1 endocrine treatment to receive fulvestrant at 500 mg plus 125 mg / day of palbociceb every three weeks or placebo. The median follow-up was 44.8 months and the results showed an improvement in

overall survival by 6.9 months by the addition of palbociceb to fulvestrant compared to fulvestrant alone. [3]

Ribociclib has been approved as a treatment for postmenopausal women with advanced HER2-negative or metastatic HR + breast cancer in combination with an aromatase inhibitor as initial endocrine therapy. The FDA has further expanded the indication for Ribociclib in combination with an AI for pre- / perimenopausal with HER2-negative or metastatic breast cancer as endocrine initial therapy. Ribociclib was approved in combination with fulvestrant for postmenopausal women with HER2-negative or metastatic breast cancer as initial endocrine-based therapy or following disease progression on endocrine therapy. The initial approval of Ribociclib was based on MONALEESA-7, a randomized, double-blind, placebo-controlled trial. The results of the trial estimated a median progression-free survival of 27.5 months for patients in the ribociclib arm versus 13.8 months for those in the placebo arm.

The efficacy of ribocycline in combination with fulvestrant was demonstrated in MONALEESA-3, a double-blind, randomized, placebo-controlled, ribociclib-plus fulvestrant combination study in 726 postmenopausal women with HR-positive, HER2-negative, The estimated mean progression-free survival was 20.5 months for patients who were treated with ribocilib as compared to 12.8 months for placebo arm. The most common adverse effects included neutropenia, nausea, infection, fatigue, diarrhea, leucopenia, vomiting, alopecia, headache, and constipation, rash and cough [4]. Abemaciclib was approved in combination with an aromatase inhibitor as the initial endocrine therapy for postmenopausal women with HER2 + advanced or metastatic breast cancer. The approval was based on the MONARCH 3 trial, a double-blind, placebo-controlled, multicenter randomized (2: 1) study in postmenopausal women with HR +, HER2-negative or metastatic breast cancer. A total of 493 patients were randomized to receive either 150 mg abemaciclib or placebo orally twice daily plus letrozole or anastrozole. The prognostic median progression free survival (PSF), was 28.2 months for patients who received abemaciclib and 14.8 months for the placebo arm. The most common side effects were diarrhea, neutropenia, fatigue, infections, nausea, vomiting, abdominal pain, anemia, and leucopenia [5].

Radiotherapy is used in stages I-III of breast cancer as adjuvant therapy following surgery to improve prognosis, but is in the metastatic settings is used for symptom palliation. Understanding the mechanisms of interaction between radiation and modern systemic therapies introduced into the metastic stage breast cancer such as chemotherapy, immunotherapy, molecular target therapies is the subject of preclinical studies designed in order to maximize the effect of radiotherapy association with systemic therapy with a limited toxicity profile. Following radiotherapy ablative doses, the release of tumor antigens, tumor DNA, cytokines and chemokines promotes intratumoral immunity. Immunomodulatory treatments, such as immune checkpoint inhibitors, could be associated with irradiation to amplify the immune antitumor response in an attempt to improve results in patients with metastatic disease. [6]

The concept of oligometastatic disease resulted in a change in treatment goals for patients diagnosed with metastatic breast cancer with a limited disease. "Oligometastases," is defined as a limited metastasis, involving one to five lesions scattered in a single site or in a reduced number of sites. It has been demonstrated that patients with <5 metastases, aggressively treated, have a better prognosis than those with> 5 metastases treated with surgical excision or radiosurgery ablation. The oligometstatic breast cancer treated with a mulimodal protocol with currative intent has an increased chances of disease control [7].

With the introduction of CDK4 / 6 inhibitors into the spectrum of systemic therapies, the problem of the association of these treatments with palliative radiotherapy or stereotactic radiotherapy for oligometastatic disease has been raised. Clinical trials demonstrating the feasibility of concomitant treatments are limited. Meattini and collaborates report a batch of 5 patients treated with RT with palliation concurrently with ribociclib plus letrozole as a first-line treatment for MBC at the Radiation Oncology Unit of Florence University [8].

Discussion

Sixteen MBC patients were included in a study and were treated with CDK4 / 6 inhibitors concomitantly with radiotherapy (RT). Thirteen patients (81.3%) received palbociclib, and three patients (18.7%) patients received ribociclib concomitant with RT. 68.7% received palliative radiotherapy in the bones sites (median dose 30Gy, range 8-36Gy), and five patients (31.2%) were treated at higher doses for oligo-metastatic sites (median dose = 50 Gy, interval 39.6-60 Gy). Neutropenia was common (Grade 2 = 12.5%, Grade 3 = 25%, and Grade 4 = 6.3%). The authors conclude that concomitant treatment of CDK4 / 6 and radiotherapy seems to be well tolerated but an increased rate of toxicity, particularly neutropenia was observed [9].

The most common haematological abnormalities observed with CDK4 / 6 inhibitors are not complicated (febrile neutropenia rate is reduced) and can be managed relatively easy by dose adjustments. Cytopenias are less common with abemaciclib, although fatigue and gastrointestinal toxicity are more common associated with this treatment. This could be an argument for the choice of abemaciclib in patients at high risk for neutropenia or who have a large part of the hematogenic marrow contained in the irradiation field. Also palbociclib and ribociclib could be preferred in case of irradiation of bone metastases in vicinity of small bowel in oder to reduce digestive toxicity [10, 11].

Cowdhary et al. included patients who received RT for symptomatic metastases concurrently or within 14 days of palbociceb. Four patients received palbociceb prior to RT (25.0%), 5 concomitantly (31.3%) and 7 after RT (43.8%). The median interval from the closest use of palbocice at RT was 5 days (range, 0-14). 11 patients were irradiated palliative on sites in the axial skeleton, 4 patients were irradiated on the pelvis and pelvis, and 3 patients received RT on the extremities. Pain reduction was performed in all patients and all degrees of hematological toxicity, except for 2 (grade 2), were of grade 1. The authors conclude that the use of association between RT and palbociclib is associated with grades 1 to 2 and no grade 3+ haematological toxicity [12].

Conclusion

CDK4 / 6 inhibitors are now part of MBC management and association with stereotactic ablative radiotherapy for oligometastatic disease but also with palliative radiotherapy become more common. Taking into account the toxicity profile of new therapies, it is necessary to identify the optimal treatment sequence to obtain the best therapeutic response. Preclinical studies are needed to demonstrate the theoretical concepts based on cell-pathway pathways on the association of CDK4 / 6 with radiotherapy and to facilitate translation of these therapies in daily clinical practice.

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